

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
1 April 2004 (01.04.2004)

PCT

(10) International Publication Number
WO 2004/026330 A1

- (51) International Patent Classification²: A61K 38/17 (74) Common Representative: K.U. LEUVEN RESEARCH AND DEVELOPMENT; Dr. Ivo Roelants- IPR Officer, Groot Begijnhof 58-59, B-3000 Leuven (BE).
- (21) International Application Number: PCT/BE2003/000158 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 23 September 2003 (23.09.2003) (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 0222014.3 23 September 2002 (23.09.2002) GB
- (71) Applicants (*for all designated States except US*): K.U. LEUVEN RESEARCH AND DEVELOPMENT [BE/BE]; Groot Begijnhof 58-59, B-3000 Leuven (BE). AARHUS UNIVERSITET [DK/DK]; Nordre Ringgade 1, DK-8000 Aarhus C (DK). AARHUS UNIVERSITY HOSPITAL [DK/DK]; Aarhus Amt, Lyseng Allé 1, DK-8270 Højbjerg (DK).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): VAN DER BERGHE, Greta [BE/BE]; Rue de Beaumont 77, B-1390 Grez-Doiceau (BE). THIEL, Steffen [DK/DK]; Nordtøftevej 11, DK-8240 Risskov (DK). KRARUP HANSEN, Troels [DK/DK]; Bygvangen 20, DK-8200 Aarhus N (DK).
- Declaration under Rule 4.17:
— of inventorship (Rule 4.17(iv)) for US only
- Published:
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/026330 A1

(54) Title: METHODS AND PREPARATIONS FOR CURING CRITICALLY ILL PATIENTS

(57) Abstract: The present invention pertains to the use of a blood mannan-binding lectin (MBL) regulator for the manufacture of a life saving drug to treat or cure a critically ill patient. It further involves the use of measurements of MBL to predict mortality in critically ill ICU patients. One further aspect of present invention is to the use of monomers and oligomers of MBL in prophylactic and/or curative treatment of patients admitted to intensive care units (ICUs).

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/BE 03/00158

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/17 A61P00/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	GARRED PETER ET AL: "Association of mannose-binding lectin polymorphisms with sepsis and fatal outcome, in patients with systemic inflammatory response syndrome." THE JOURNAL OF INFECTIOUS DISEASES. UNITED STATES 1 NOV 2003, vol. 188, no. 9, 1 November 2003 (2003-11-01), pages 1394-1403, XP009024751 ISSN: 0022-1899 the whole document -/-	1-48

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

28 January 2004

Date of mailing of the international search report

18/02/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3015

Authorized officer

Fayos, C

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/BE 03/00158

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 24919 A (LEUVEN K U RES & DEV ; DEN BERGHE GRETA HERMAN VAN (BE); ZEGHER FRA) 21 September 1995 (1995-09-21) claims 1,5 page 3, line 33 - line 36 examples 1-7 ----	1-9,11, 12, 17-21, 35-38
X	WO 99 64453 A (STATENS SERUMINSTITUT ;LAURSEN INGA (DK)) 16 December 1999 (1999-12-16) claims 24-26 page 17, line 16 - line 34 ----	1-48
X	WO 02 05833 A (FISCHER PER ; NATLMMUNE APS (DK)) 24 January 2002 (2002-01-24) the whole document ----	1-48
X	KILPATRICK DAVID C: "Mannan-binding lectin: clinical significance and applications." BIOCHIMICA ET BIOPHYSICA ACTA. NETHERLANDS 19 SEP 2002, vol. 1572, no. 2-3, 19 September 2002 (2002-09-19), pages 401-413, XP004380529 ISSN: 0006-3002 the whole document in particular 5. p 408-409 ----	1-48
Y	WO 00 24398 A (BRISTOL MYERS SQUIBB CO) 4 May 2000 (2000-05-04) claims 14,15 ----	1-9,11, 12, 17-21, 35-38
Y	HIBBERD M L ET AL: "Variation in the mannose binding lectin (MBL) gene and susceptibility to sepsis" SEPSIS 2001 NETHERLANDS, vol. 4, no. 3, 2001, pages 201-207, XP009024789 ISSN: 1385-0229 page 203, column 2, paragraph 3 -page 204, column 2, paragraph 6 abstract ---- -/--	1-48

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/BE 03/00158

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HANSEN TROELS KRARUP ET AL: "GH strongly affects serum concentrations of mannan-binding lectin: Evidence for a new IGF-I independent immunomodulatory effect of GH" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, vol. 86, no. 11, November 2001 (2001-11), pages 5383-5388, XP002268239 ISSN: 0021-972X the whole document	1-9, 11, 12, 17-21, 35-38
Y	--- GARRED P ET AL: "Association of mannose-binding lectin gene heterogeneity with severity of lung disease and survival in cystic fibrosis." THE JOURNAL OF CLINICAL INVESTIGATION. UNITED STATES AUG 1999, vol. 104, no. 4, August 1999 (1999-08), pages 431-437, XP002268240 ISSN: 0021-9738 abstract discussion	1-48
P,X	--- HANSEN TROELS KRARUP ET AL: "Intensive insulin therapy exerts antiinflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels." THE JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM. UNITED STATES MAR 2003, vol. 88, no. 3, March 2003 (2003-03), pages 1082-1088, XP009024778 ISSN: 0021-972X the whole document	1-48
P,X	--- GARRED PETER ET AL: "Association of mannose-binding lectin polymorphisms with sepsis and fatal outcome in patients with systemic inflammatory response syndrome." MOLECULAR IMMUNOLOGY, vol. 40, no. 2-4, September 2003 (2003-09), page 206 XP009024781 9th European Complement Workshop; Trieste, Italy; September 06-09, 2003 ISSN: 0161-5890 (ISSN print) abstract	1-48
P,Y	--- WO 03 010188 A (MATTHIESEN FINN ; NATIMMUNE AS (DK)) 6 February 2003 (2003-02-06) claims 37-49 page 25, line 20 -page 26, line 3 --- -/--	1-48

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/BE 03/00158

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	<p>EP 1 344 533 A (NATIMMUNE AS) 17 September 2003 (2003-09-17) page 14, paragraph 141 -page 1, paragraph 150 claims 45-51</p>	1-48

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application

PCT/BE 03/00158

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9524919	A	21-09-1995	AU 1942995 A WO 9524919 A1 NL 9401045 A	03-10-1995 21-09-1995 02-10-1995
WO 9964453	A	16-12-1999	AU 764066 B2 AU 4134399 A CA 2334696 A1 WO 9964453 A1 EP 1084143 A1 JP 2002517513 T NZ 509089 A US 6429192 B1	07-08-2003 30-12-1999 16-12-1999 16-12-1999 21-03-2001 18-06-2002 25-10-2002 06-08-2002
WO 0205833	A	24-01-2002	AU 7841601 A WO 0205833 A1 EP 1303288 A1	30-01-2002 24-01-2002 23-04-2003
WO 0024398	A	04-05-2000	AU 749970 B2 AU 1598300 A CA 2348023 A1 EP 1126854 A1 JP 2002528417 T WO 0024398 A1 US 6380184 B1	04-07-2002 15-05-2000 04-05-2000 29-08-2001 03-09-2002 04-05-2000 30-04-2002
WO 03010188	A	06-02-2003	WO 03010188 A1	06-02-2003
EP 1344533	A	17-09-2003	WO 03077937 A1 EP 1344533 A1 US 2004006009 A1	25-09-2003 17-09-2003 08-01-2004

PCT/BE 03/00158

Sheet No. 5

Box No. VIII (iv) DECLARATION: INVENTORSHIP (only for the purposes of the designation of the United States of America)
The declaration must conform to the following standardized wording provided for in Section 214; see Notes to Boxes Nos. VIII, VIII (i) to (iv) (in general) and the specific Notes to Box No. VIII (iv). If this Box is not used, this sheet should not be included in the request.

Declaration of inventorship (Rules 4.17(iv) and 51bis.1(a)(iv))
for the purposes of the designation of the United States of America:

I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.

This declaration is directed to the international application of which it forms a part (if filing declaration with application).

This declaration is directed to international application No. PCT/BE 03/00158 (if furnishing declaration pursuant to Rule 26ter).

I hereby declare that my residence, mailing address, and citizenship are as stated next to my name.

I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.

Prior Applications: 23 September 2002 - 0222014.3 - GB

I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

VAN DEN BERGHE Greta

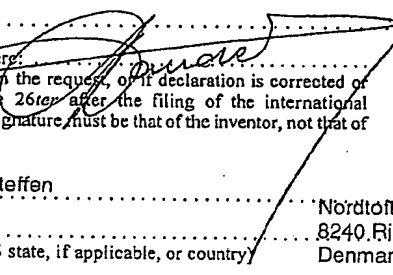
Name: rue de Beaumont 77

Residence: 1390 Grez-Doiceau

(city and either US state, if applicable, or country) Belgium

Mailing Address:

Citizenship: BE

Inventor's Signature:  Date: 06/10/03
(if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent) (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

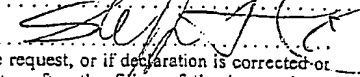
Name: THIEL Steffen

Residence: Nordtøftvej 11

(city and either US state, if applicable, or country) 8240 Risskov

Mailing Address: Denmark

Citizenship: DK

Inventor's Signature:  Date: 19/10/03
(if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent) (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

☒ This declaration is continued on the following sheet, "Continuation of Box No. VIII (iv)".

Continuation of Box No. VIII (i) to (v) **DECLARATION**

If the space is insufficient in any of Boxes Nos. VIII (i) to (v) to furnish all the information, including in the case where more than two inventors are to be named in Box No. VIII (iv), in such case, write "Continuation of Box No. VIII..." (indicate the item number of the Box) and furnish the information in the same manner as required for the purposes of the Box in which the space was insufficient. If additional space is needed in respect of two or more declarations, a separate continuation box must be used for each such declaration. If this Box is not used, this sheet should not be included in the request.

INVENTORS

KRARUP HANSEN Troels
Bygvangen 20
8200 Aarhus N
Denmark

Signatures



Date

22/10/03